Imugene Limited

IMU.131.203

nextHERIZON: AN OPEN-LABEL, SIGNAL GENERATING, PHASE 2 STUDY OF HER-VAXX IN COMBINATION WITH CHEMOTHERAPY OR PEMBROLIZUMAB IN PATIENTS WITH METASTATIC HER2/NEU OVER-EXPRESSING GASTRIC OR GASTROESOPHAGEAL JUNCTION (GEJ) ADENOCARCINOMAS WHO HAVE PREVIOUSLY RECEIVED TRASTUZUMAB AND PROGRESSED ON THIS TREATMENT

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Final Statistical Analysis Plan

Version 1.0

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Version	Date Issued	SAP Section	Detail of Changes
1.0	08Nov2023	All Sections	Final Version

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List of Abbreviations

AE	Adverse Event
AECI	Adverse Event of Clinical Interest
AESI	Adverse Events of Special Interest
AGC	Advanced Gastric Cancer
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSA	Body Surface Area
C1D1	Cycle 1 Day 1
CI	Confidence Interval
CRF	Case Report Form
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DoR	Duration of Response
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
EAS	Evaluable Analysis Set
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EoT	End of treatment
FAS	Full Analysis Set
FU	Follow Up
GEJ	Gastroesophageal Junction
IB	Investigator's Brochure
GC	Gastric Cancer
GM	Geometric Mean
GMT	Geometric mean titer
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hazard Ratio
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICIs	Immune Checkpoint Inhibitors
IM	Intramuscular(ly)
IMP	Investigational Medicinal Product
IMU	Imugene Limited, Australia
IMU-131	Investigational product consisting of P467-CRM in Montanide adjuvant
irAE	Immune related AE
KM	Kaplan-Meier
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
mGC	Metastatic Gastric Cancer
mL	Milliliter
MUGA	Multiple Gated Acquisition (scan)

N	Number
NGS	Next Generation Sequencing
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD	Protocol Deviation
PD-L1	Programmed death-ligand 1
PFS	Progression Free Survival
PR	Partial Response
PT	Preferred Term
Q1	Quartile 1
Q3	Quartile 3
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SD	Stable Disease
SD	Standard Deviation
SOC	System Organ Class
SoC	Standard of Care
SRC	Safety Review Committee
TEAE	Treatment-Emergent Adverse Events
TMB	Tumor mutational burden
µg	Microgram
UK/UNK	Unknown
WHO	World Health Organization

1. Introduction

This Statistical Analysis Plan (SAP) defines the statistical methods and data presentations to be used by PPD Biostatistics department in the analysis and presentation of data for the analysis of Imugene Limited study number IMU.131.203, entitled "nextHERIZON: An open-label, signal generating, phase 2 study of HER-Vaxx in Combination with chemotherapy or pembrolizumab in patients with metastatic HER2/neu over-expressing gastric or gastroesophageal junction (GEJ) adenocarcinomas who have previously received trastuzumab and progressed on this treatment".

The investigational product, IMU-131, which is composed of 3 individual B-cell epitopes (P467) selected from Human epidermal growth factor receptor 2 (HER2/neu) structure and conjugated to CRM197, which becomes HER-Vaxx when emulsified with excipient Montanide (ISA 51 VG Sterile). IMU- 131 induces the patient's own B cells to produce endogenous anti-HER2/neu antibodies. HER-Vaxx (IMU-131) is being developed for the treatment of patients with HER2/neu overexpressing metastatic or advanced adenocarcinoma of the stomach or GEJ (referred to as advanced gastric cancer [AGC]).

Pembrolizumab is a potent humanized Immunoglobulin G4 (IgG4) monoclonal Antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated for the treatment of patients across a number of indications.

In Phase 1, Phase 1b of clinical trial of IMU-131, a marked increase in cellular/clinical response was observed. Safety data were also well tolerated with no significant local or systemic reactions. The preliminary immunology and clinical response data from Phase 2 reveal that the addition of HER-Vaxx to chemotherapy significantly prolonged survival. Safety data of Phase 2 and Phase 2 also indicate that IMU-131 is well tolerated.

This SAP covers all specified analysis for the interim analysis based on the following documents:

- Final Protocol, Amendment 4.0, 4 June 2023
- Electronic case report form (eCRF), 06 July 2023

2. Objectives

2.1. Primary Safety Objective

- To evaluate the safety and tolerability of HER-Vaxx in combination with chemotherapy (ramucirumab plus paclitaxel) or pembrolizumab.

2.2. Primary Efficacy Objective

- To evaluate the objective response rate (ORR) of HER-Vaxx in combination with chemotherapy or pembrolizumab according to RECIST v1.1.

2.3. Secondary Objective

- To evaluate additional efficacy and survival measures (OS, progression free survival [PFS], duration of response [DoR]) of HER-Vaxx in each Arm.

2.4. Exploratory Objectives

- To evaluate humoral and cellular immunogenicity data of HER-Vaxx plus chemotherapy (ramucirumab plus paclitaxel) or pembrolizumab.
- To evaluate immunogenicity and serum and biochemical markers of tumor progression to clinical outcomes of ORR, PFS and DoR.
- To evaluate Arm-specific associations between clinical outcome and HER2/neu expression, PD-L1 expression, and TMB.

3. Investigational Plan

3.1. Overall Study Design and Plan

This study will evaluate safety and efficacy of HER-Vaxx in combination with chemotherapy (ramucirumab plus paclitaxel) or pembrolizumab in patients with metastatic GC (mGC)/GEJ cancer who have progressed on or after trastuzumab treatment.

For Arm 2, all patients must be re-assessed for their HER2/neu status prior to enrollment into the study due to potential HER2/neu loss during their previous treatment with trastuzumab (Seo, 2019). Patients must have confirmed HER2/neu overexpression since last progression by tumor biopsy (post-progression fresh or archival tissue, or post-progression pathology report). Sponsor may approve inclusion based on liquid (blood-based, ctDNA/NGS) biopsy to assess patients' HER2/neu positivity where tumor biopsy is not clinically indicated.

The study will include 2 treatment Arms that will be independently assessed for their endpoints.

- Arm 1: HER-Vaxx + chemotherapy (ramucirumab and paclitaxel)
- Arm 2: HER-Vaxx + pembrolizumab

Eligibility for Arm 1 requires patients with mGC/GEJ adenocarcinoma overexpressing HER-2/neu who have progressed on or after trastuzumab in combination with chemotherapy as first line therapy; patients that subsequently progressed on or after trastuzumab deruxtecan or another anti-HER2 treatment are eligible for enrolment in Arm 1. Arm 1 eligibility does not depend on prior treatment with immune checkpoint inhibitors (ICIs).

Eligibility for Arm 2 requires that patients be naïve to immune checkpoint inhibitors and have progressed on or after first line treatment with a HER-2 targeted therapy including trastuzumab in combination with standard of care chemotherapy.

In both Arms, HER-Vaxx may continue independently of chemotherapy or pembrolizumab until treatment discontinuation criterion is met. In Arm 1, chemotherapy may continue independently until treatment discontinuation criterion is met if HER-Vaxx has been discontinued. In Arm 2, pembrolizumab may continue independently of HER-Vaxx until treatment discontinuation criterion is met, for a maximum of 35 cycles (approximately 2 years).

For each Arm, after 8 evaluable patients are enrolled (Stage 1), if 1 or more patients respond (i.e., experience CR or PR), an additional 7 evaluable patients will be enrolled in that Arm (Stage 2). If there are no responses in Stage 1, then preliminary anti-tumor activity in the group will not have been identified and no further patients will be enrolled in that Arm. If the arm continues to Stage 2, a total of 15 evaluable patients will be studied for that Arm. The Arm will be considered successful if ≥ 4 treated patients respond, and the arm may be expanded to enroll 25 patients. This design is applied to each arm separately.

Arm 1 requires a minimum of 5 of 8 patients in Stage 1 and additional 5 patients (i.e., 10 of the total 15 patients enrolled) in Stage 2 must have HER2/neu overexpression as assessed by the central lab or post-progression pathology report.

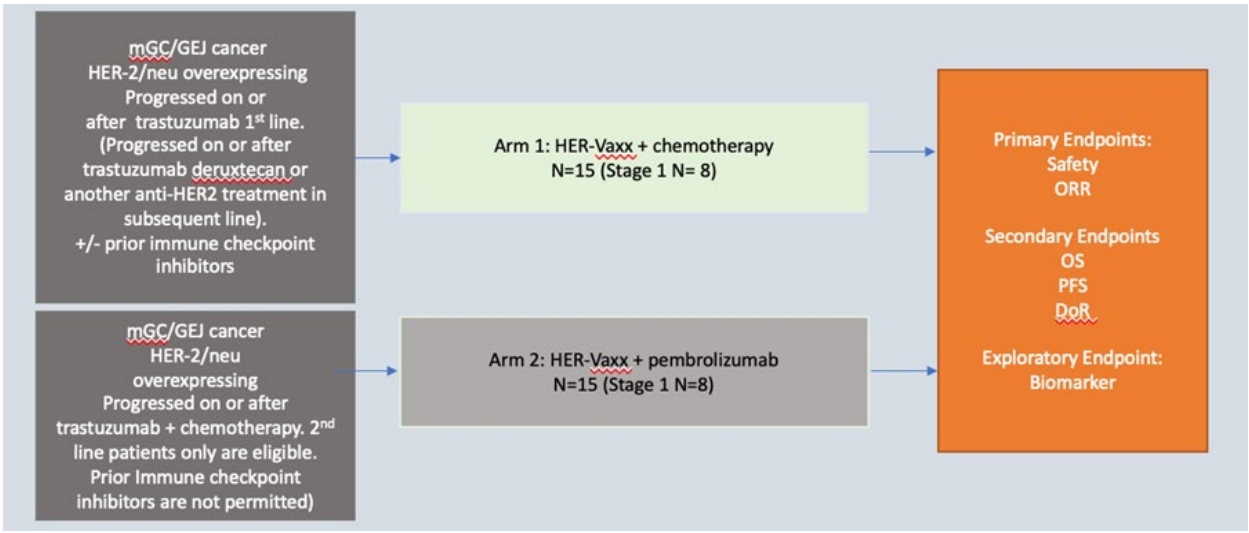
Arm 2 requires that all patients enrolled must have post-progression HER2/neu overexpression confirmed locally for eligibility and subsequently assessed by the central lab or post-progression pathology report.

Stage 1 of each arm will include a safety run-in phase with staggered enrollment, with the first 3 patients receiving their first treatment dose at least 15 days apart. After 3 patients are treated with the combination and are considered evaluable for the safety run-in period as defined below, a SRC consisting of study investigators, and Sponsor medical monitor will assess the combination to ensure an acceptable safety profile has been established before enrolling the remaining patients.

The primary objectives are to evaluate safety as well as ORR independently for each treatment arm. Additional anti-tumor activity in terms of OS, PFS and DoR serve as secondary objectives.

Exploratory objectives include biomarker evaluation and arm-specific associations of biomarkers, including humoral and cellular responses, with measures of clinical response including ORR, OS, PFS and DoR. The nextHERIZON study set up is provided in Figure 1.

Figure 1. Study Schema



Chemotherapy (ramucirumab 8 mg/kg IV on Days 8 and 22 of a 28-day cycle + paclitaxel 80 mg/m2 IV on Days 8, 15, and 22 of a 28-day cycle). ORR = objective response rate; OS = overall survival; PFS= progression free survival; DoR = duration of response.

Interim analysis is planned when 8 evaluable patients are enrolled or when stage 1 is completed for both arms patients.

3.1.1. Safety and HER2 Antibody Consideration

Both Arms will include a safety run-in phase with staggered enrollment with the first 3 patients receiving their first treatment dose at least 15 days apart. After 3 patients are treated with the combination and are considered evaluable for the safety run-in period as defined below, a SRC consisting of study investigators, and Sponsor medical monitor will assess the combination to ensure an acceptable safety profile has been established before enrolling the remaining patients.

3.1.2. Safety Evaluation for Combination in Arm 1 and Arm 2

Arm 1: HER-Vaxx in combination with chemotherapy (ramucirumab plus paclitaxel)

This combination safety evaluation will be based on three evaluable patients at a single dose level of HER-Vaxx plus chemotherapy (ramucirumab plus paclitaxel). An initial 3 patients will be treated and observed for the occurrence of DLTs for a period of 29 days (including 3 doses of HER-Vaxx and at least 1 cycle of chemotherapy). Safety data will be reviewed by the SRC before further patients are enrolled.

Arm 2: HER-Vaxx in combination with pembrolizumab

This combination safety evaluation will be based on three evaluable patients at a single dose level of HER-Vaxx plus pembrolizumab. An initial 3 patients will be treated and observed for the occurrence of DLTs for a period of 29 days (including 3 doses of HER-Vaxx and at least 1 dose of pembrolizumab). Safety data will be reviewed by the SRC before further patients are enrolled.

Safety data from both Arms will be reviewed by the SRC on an ongoing basis for the duration of the study.

The decision to continue enrollment or extend the safety run-in will be taken by the SRC after reviewing all available safety data (including DLTs) from the first 3 evaluable patients that are part of the safety run-in and have completed the DLT observation period. The safety run-in can be extended by another 3 patients, or all additional patients can be enrolled for Stage 1 based on the occurrence of DLTs.

On an on-going basis, the SRC will review the safety data and make recommendations on the continuation of the study following the procedures outlined in the SRC charter.

The SRC is comprised of study investigators and Sponsor medical monitor. All decisions will be documented in the form of minutes.

Based on the review of available data on safety, the SRC will make recommendations regarding further conduct and the scientific and ethical integrity of the study. The SRC will provide one of the following recommendations:

- Arm 1 / Arm 2 is to be continued
- Arm 1 / Arm 2 is to be stopped
- Modification of the study to address safety and dosing issues.

3.2. Study Endpoints

3.2.1. Primary Safety Endpoints

- Frequency and severity of adverse events (AEs) graded by Common Terminology Criteria for Adverse Events (CTCAE) v5.0.
- Frequency and severity of immune-related AEs.
- Frequency of patients discontinuing study treatment due to AEs.
- Changes and shifts from baseline in clinical laboratory, vital signs, echocardiogram or multiple gated acquisition (MUGA) scan and electrocardiogram (ECG) parameters.

3.2.2. Primary Efficacy Endpoint

- ORR measured from baseline as the proportion of patients achieving a confirmed best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1 based on local review.

3.2.3. Secondary Efficacy Endpoints

- DoR measured from earliest CR or PR until first documentation of PD based on RECIST v1.1 or death due to any cause.
- PFS defined as the time from first dose of study treatment to first documentation of progressive disease (PD) based on RECIST v1.1, or to death from any cause.
- OS defined as the time from first dose of study treatment to death from any cause.

3.2.4. Exploratory Endpoints

- Values and changes from baseline in humoral and cellular immunogenicity including P467-specific antibodies, HER2-specific antibodies, vaccine-specific cytokine levels and regulatory and effector T and B cells.
- Evaluation and Arm-specific associations of serum and biochemical markers of tumor progression and immunogenicity, including humoral and cellular responses, with measures of clinical response including ORR, OS, PFS and DoR.
- Analysis of HER2/neu expression, PD-L1 expression and TMB in pre- and post-treatment tumor biopsies / liquid biopsies (circulating tumor DNA [ctDNA]/next generation sequencing [NGS]).

3.3. Treatments

The following treatment supplies will be used in the study:

Product	Supplied as:
HER-Vaxx	The dose of HER-Vaxx to be used in combination with chemotherapy or pembrolizumab will 100 µg. A 1.0ml volume of HER-Vaxx will be administered Intramuscular(ly) (IM) on Days 1, 15, 29 and 57 and then every 63 days until treatment discontinuation criterion is met
Ramucirumab + Paclitaxel	Patients in Arm 1 will receive intravenous (IV) administration of chemotherapy (ramucirumab 8 mg/kg IV on Days 8 and 22 + paclitaxel 80 mg/m2 IV on Days 8, 15, and 22 of a 28-day cycle).
Pembrolizumab	The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W) starting on Day 8.

3.4. Dose Adjustment/Modifications

Dose modification/adjustment are allowed in this study based on Immune related AEs, infusion-reactions, patient conditions, cumulative toxicities, etc. The details are given in 6.3 of Protocol.

4. General Statistical Considerations

Continuous data will be described using descriptive statistics (i.e., n, mean, standard deviation, median, minimum, and maximum). Categorical data will be described using the patient count and percentage in each category. For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. Standard deviation / standard error will be displayed to two levels of precision greater than the data collected.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for missing values. The denominator for all percentages will be the number of patients within the analysis set of interest, unless otherwise specified. Percentages will be presented to one decimal place except for the display of 100% frequency which will be displayed as ‘XX (100)’.

Data will be displayed in all listings sorted by treatment arm, patient number and visit, if applicable. Listings will include all visits including unscheduled visits.

The arms will be displayed as:

- Arm 1: HER-Vaxx + chemotherapy (ramucirumab and paclitaxel)
- Arm 2: HER-Vaxx + pembrolizumab

Due to a smaller number of patients in any of the arms, it might be possible that table and figure will have only one arm displayed, the details of the same are mentioned in respective sections.

Along with the treatment arms, "Overall" column will also be displayed for the overall patients in both of the arms in all safety tables, unless otherwise stated.

"No data available for this report" will be presented when there are no data available to report.

Unless otherwise specified, baseline will be defined as the last non-missing observation prior to first dose of study treatment. Study day is defined as:

- Visit/examination date – date of first study treatment administration when date is prior to the date of first study treatment administration (day 1).
- Visit/examination date – date of first study treatment administration + 1 when date is after day 1

For summaries by visit, if multiple records fall on the same visit, then the record which is closest to the target visit will be considered. In case of a tie, the record with the earlier date will be chosen. If multiple records on same day, will consider the latest record. Unless otherwise specified, unscheduled and early discontinuation results will not be summarized but will be listed.

The end of treatment visit date is defined as the last dose date + 30 days in case if end of treatment visit date is missing. The end of the study is defined as the date mentioned in End of Study eCRF page.

For the purpose of inclusion in tables, incomplete start and stop dates (e.g., AEs and prior/concomitant medication) will be imputed as follows:

Missing start dates (where UK and UNK indicate unknown or missing day and month respectively) will be handled as follows:

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study treatment, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study treatment month and year and the stop date (after any imputation) is on or after the first dose of study treatment, then assume the date of the first dose of study treatment. If the month and year are the same as the first dose of study treatment month and year and the stop date (after any imputation) is prior to the first dose of study treatment, then assume the stop date for the start date;
- UK-UNK-YYYY: If the year is different from the year of first dose of study treatment, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study treatment year and the stop date (after any imputation) is on or after the first dose of study treatment, then assume the date of the first dose of study treatment. If the year is the same as the first dose of study treatment and the stop date (after any imputation) is prior to the first dose of study treatment, then assume the stop date for the start date.

Missing stop dates (where UK and UNK indicate unknown or missing day and month respectively) will be handled as follows:

- UK-MMM-YYYY: Assume the last day of the month;
- UK-UNK-YYYY: Assume 31-DEC-YYYY.

If a patient dies during the study and the AE is ongoing at the time of death, then the stop date will set to missing.

In case of missing historical dates which happened before treatment start date, such as initial cancer diagnosis date, the missing dates will be handled as follows

- UK-MMM-YYYY: Assume the 1st day of the month;
- UK-UNK-YYYY: If the year is same as the year of first dose of study treatment, assume 01-JAN-YYYY of the collected year, else assume 01-JUL-YYYY in case if year is different from first dose of study treatment.

4.1. Sample Size

The study plans to enroll 15 evaluable patients into each Arm of the study, for a total of approximately 30 evaluable patients.

For each Arm, after 8 evaluable patients are enrolled (Stage 1), an additional 7 evaluable patients will be enrolled in that group (Stage 2) if 1 or more patients respond (i.e., experience CR or PR). If there are no responses in Stage 1, then preliminary anti-tumor activity in the group will not have been identified and no further patients will be enrolled in that Arm. If the Arm continues to Stage 2, a total of 15 evaluable patients will be studied for that Arm. The Arm will be considered successful if ≥ 4 treated patients respond and the Arm may be expanded to enroll 25 patients. This design is applied to each Arm separately and is based on a 2-stage Simon Minimax design for a total of 15 evaluable patients (null hypothesis that ORR ≤ 11% versus the alternative hypothesis that ORR ≥ 40% with alpha=0.07268 and power=90.463%).

4.2. Randomization and Blinding

This is an open-label non-randomized study. Randomization and blinding are not applicable.

4.3. Analysis Set

The following analysis population sets will be used in this study:

4.3.1. All Enrolled Set

The all enrolled set will comprise of all patients who sign an ICF.

4.3.2. Safety Analysis Set

The safety analysis set (SAF) consists of all patients who receive at least one dose of study treatment (HER-Vaxx). All safety and tolerability evaluations will be based on this analysis set. Patients will be analyzed according to the actual treatment arm.

4.3.3. Full Analysis Set

The full analysis set (FAS), which includes all enrolled patients who receive at least 1 administration of study treatment (HER-Vaxx), will be used for analyses of OS and may be used for additional analyses of selected efficacy and exploratory endpoints. Patients will be analyzed according to the planned treatment arm.

4.3.4. Evaluable Analysis Set

The evaluable analysis set (EAS), which includes all patients who receive at least 1 administration of study treatment and have an evaluable baseline tumor assessment and who have at least one evaluable post-baseline tumor response assessment as per RECIST v1.1 or were discontinued due

to toxicity, will be the primary analysis set for analyses of response-based anti-tumor activity endpoints. Patients will be analyzed according to the planned treatment arm.

5. Patient Disposition

5.1. Disposition

A summary of the analysis sets based on all enrolled set includes the number and percentage of patients for the following categories: all enrolled set, safety analysis set, full analysis set and evaluable analysis set. All percentages will be based on the number of patients in safety analysis set. A listing will be presented by patients for showing each patient in which analysis population set they are included. Screen failure patients will also be presented in this listing.

Patient disposition will be summarized by treatment arm and overall using all enrolled set. A disposition of patients includes the number of screen failure patients, number of patients who received at least one dose of study treatments (HER-Vaxx) and the number and percentage of patients for following categories: patients who completed study treatment, patients who discontinued study treatment, patients who completed the study, patients who discontinued from the study and survival status at end of study.

The primary reasons for study treatment discontinuation and study participation discontinuation will also be summarized in this table.

Patient disposition listing will be presented by treatment arm using all enrolled set.

5.2. Protocol Deviations

The number and percentage of patients with significant protocol deviation will be summarized for Arm 1. Protocol deviations will be listed with date of occurrence, deviation category, deviation. All summaries will be performed by treatment arms using the safety analysis set and listing will be based on all enrolled set.

6. Demographics and Baseline Characteristics

A summary of demographics and baseline information will be presented by treatment arms using safety analysis set.

6.1. Demographics

The demographic characteristics consist of age (years), gender, child-bearing potential, height (cm), weight (kg), BMI (kg/m^2), ethnicity and race.

Age (years), height (cm), weight (kg) and BMI (kg/m^2) will be summarized using descriptive statistics. The number and percentage of patients by gender (Male, Female), child-bearing potential (Yes, No), ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown), race (Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, White, Other and Not reported) will also be summarized. Percentages will be based on the total number of patients in the safety analysis set except for fertility status which will be based on the number of female patients.

6.2. Baseline Characteristics

Summary for the following disease characteristics will be provided:

- Baseline Eastern Cooperative Oncology Group (ECOG) performance status
- Baseline left ventricular ejection function (LVEF)
- HER2 Status (HER2++ or HER2+++ vs HER2+)
- Prior Lines of Treatment (≤2 vs ≥3)
- Prior use of ENHERTU treatment (Yes vs No)

Demographic and baseline characteristics will be presented in listings using safety analysis set.

6.3. Medical History

6.3.1. General Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 25.0. The number and percentage of patients with any medical history will be summarized by Arm 1, for each system organ class and preferred term. Percentages will be calculated based on number of patients in the safety analysis set.

Patient medical history data including specific details will be presented in a listing using safety analysis set. All summaries will be performed by treatment arm using the safety analysis set.

6.3.2. Oncology and Surgical History

The number and percentage of patients includes following categories related to oncology history will be summarized by Arm 1 using safety analysis set.

- Time from initial gastric cancer diagnosis to start of study treatment (as categories: <1 month, 1- <6 months, 6- <12 months, ≥12 months): Date of first dose - Date of initial gastric cancer diagnosis in months.
- Initial tumor diagnosis type (Gastroesophageal junction (GEJ) adenocarcinoma, Gastric adenocarcinoma)
- Overall stage at diagnosis (0, IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV)
- Time from last disease progression prior to screening to start of study treatment (as categories: <1 month, 1- <6 months, 6- <12 months, ≥12 months): Date of first dose - Date of last disease progression prior to screening.
- Disease extent at initial diagnosis (Resectable, Borderline Resectable, Unresectable locally advanced, Unresectable and metastatic)
- Tumor grade at screening (Tumor grade 3, Tumor grade 4)
- Primary tumor (Tx, T0, Tis, T1, T2, T3, T4)
- Regional lymph nodes (Nx, N0, N1, N2, N3)
- Distant metastasis (Mx, M0, M1)

The number and percentage of patients includes following categories related to prior surgery will be summarized by Arm 1 using safety analysis set.

- Any prior surgery for gastric cancer (yes, no)
- Any surgery for gastric cancer (yes, no)
- Type of Surgical Procedure (Endoscopic resection, Subtotal (partial) gastrectomy, Total gastrectomy, Placement of a feeding tube, Lymph node removal, Palliative surgery for unresectable cancer, Other)
- Time from surgery to start of study treatment (as categories: <1 month, 1- <6 months, 6- <12 months, ≥12 months): Date of first dose - Date of surgery in months.

All oncology history data will be listed by treatment arms and patient using the safety analysis set. To calculate duration in months, days will be converted to months by dividing the number of days by 30.4375.

6.4. Inclusion and Exclusion Criteria

The details of the inclusion and exclusion criteria can be found in Sections 4 of the protocol. The patients who have not met eligibility criteria will be listed using enrolled population along with their details of inclusion criteria not met and/or exclusion criteria met.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

All prior and concomitant medications will be coded using World Health Organization Drug Dictionary (WHODRUG Version B3-March 2022). The total number of prior and/or concomitant medications and the number and percentages of patients with at least one prior and/or concomitant medication will be summarized by Arm 1. The number and percentages of patients with all prior and/or concomitant medications will be summarized by treatment arm and overall, by Anatomical Therapeutic Chemical (ATC) and preferred term. If the ATC level 4 for the drug class is not available, level 3 will be used instead. Prior and/or concomitant medications will be presented in a listing. All summaries and listing will be performed using the safety population.

A prior medication is defined as any medication started and ended prior to the first study treatment. A concomitant medication is defined as any medication started or continuing or ended after first dose of study treatment up to 30 days after the last dose of study treatment.

In instances where a medication start date is incomplete, it will be conservatively imputed to determine whether or not the medication was prior or concomitant. If the start date and end date are missing, then it will be assumed to be concomitant. Imputation details for missing concomitant medication start and end date are presented in Section 4.

Prior and concomitant medications will be listed by treatment arms using safety analysis set.

7.2. Prior and Concomitant Drug Therapies and Medications

All prior and concomitant systemic therapies and medications will be coded and analyzed similar to Section 7.1 .

Prior therapies and medications are those with the start and stop dates prior to the first dose of the study; while concomitant systemic therapies and medications are those with start or stop dates after the first dose of the study. Partial dates will be imputed as per algorithm presented in Section 4.

Other details include time from last therapy to start of study treatment (as categories: <1 month, 1- <6 months, 6- <12 months, ≥12 months), regimen number, best overall response and reason drug stopped will be summarized with number of patients and percentage by Arm 1. All available information related to systemic therapies will be listed separately, by each treatment arms and patient using the safety analysis set.

7.3. Prior and Concomitant Radiotherapy

The number and percentage of patients having prior radiation therapy or concomitant radiotherapy, location, primary reason for radiotherapy will be summarized by Arm 1. The numeric results include total dose received will be summarized descriptively by Arm 1, and related details will be listed separately by each treatment arms and patient using the safety analysis set.

7.4. Concomitant Procedure/Surgery

Concomitant Procedure/Surgery will be coded using Version 25.0 of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients with concomitant procedures coded to each MedDRA system organ class (SOC) and preferred term (PT) along with reason of procedure will be summarized by Arm 1 and listed by treatment arms using the safety analysis set. At each level of summarization, a patient is counted once if the patient reported one or more procedure at that level.

7.5. Study Treatments

7.5.1. Extent of Exposure

The following will be summarized using descriptive statistics:

- Duration of HER-Vaxx (weeks) will be calculated as ((last HER-Vaxx dose date - HER-Vaxx start date + 1)/7)
- Duration of exposure (weeks) will be calculated as ((maximum of end date (HER-Vaxx, Ramucirumab, Paclitaxel, Pembrolizumab) - HER-Vaxx start date + 1)/7)

For patients who are still treatment ongoing at the clinical cutoffs, the end date will be earlier date of the clinical cutoff date and the maximum date among the exposure data captured on the HER-Vaxx/ Ramucirumab/ Paclitaxel/ Pembrolizumab Administration eCRF pages depends upon the summary.

- Number of patients started Cycle 1, Cycle 2, Cycle 3 and so on will be presented by count and percentage
- Number of patients completed Cycle 1, Cycle 2, Cycle 3 and so on, will be presented by count and percentage
- Number of HER-Vaxx doses
- Cumulative actual total volume of HER-Vaxx (mL) administered

- Cumulative actual total volume of Ramucirumab (mL) administered
- Cumulative actual total volume of Paclitaxel (mL) administered
- Cumulative actual total volume of Pembrolizumab (mL) administered

All summaries and listings will be performed by treatment arms using the safety analysis set.

8. Efficacy Analysis

The objective of efficacy analysis in this study is to assess the objective response rate (ORR) and survival measures (Overall Survival [OS], progression free survival [PFS], duration of response [DoR]) of HER-Vaxx in combination with chemotherapy or pembrolizumab. Tumor response assessment will be based on RECIST v1.1 according to the Schedule of Events given in Appendix 13.2.

All the summary of primary and secondary efficacy analysis will be presented for Arm 1 using evaluable analysis set, while listing will be for both treatment arms using full analysis set, unless otherwise stated.

8.1. Primary Efficacy Endpoint

The primary efficacy endpoint is objective response rate (ORR). The confirmed best overall response for each patient will be derived using algorithm given in Appendix 13.1.

8.1.1. Objective Response Rate

The objective response rate (ORR) is defined as the proportion of patients achieving a confirmed best overall response of complete response (CR) or partial response (PR) according to RECIST v1.1 based on local review prior to disease progression or initiation of further anti-cancer therapy during the study treatment period across all the time points. The non-responders (including missing or unknown best objective response (BOR) patients) also be included in denominator.

The overall response rate will be summarized by using binomial response rates and their corresponding two-sided 95% exact confidence intervals using the Clopper-Pearson method by Arm 1 using evaluable analysis set.

8.2. Secondary Efficacy Endpoint

All radiographic assessment will be done according to Response Evaluation Criteria in Solid Tumors version v1.1 (RECIST v1.1).

8.2.1. Duration of Response

Duration of response will be calculated in weeks and is defined as the time from the first observation of CR or PR to first documented progressive disease (PD), or death due to any cause. Duration of response will be censored at the last adequate tumor assessment date if the patient has not progressed, or the last assessment showing non-PD or unconfirmed PD.

Duration of response will each be summarized using the Kaplan-Meier method by Arm 1. The median survival times will be estimated by the Kaplan-Meier method and presented along with their corresponding 95% CI. The 25^{th} percentile and 75^{th} percentile for the survival times along with the corresponding 95% CI for the percentiles will also be displayed, CI will be calculated using Brookmeyer and Crowley method. Kaplan-Meier curves will also be produced.

The same summary including KM plot for duration of response will be repeated for subgroup HER2 status (HER2++ or HER2+++ vs HER2+), prior lines of treatment (≤2 vs ≥3) and prior use of ENHERTU treatment (Yes vs No).

8.2.2. Progression Free Survival

Progression Free Survival (PFS) will be calculated in weeks and is defined as the time from the first dose date of study treatment to first observation of documented progressive disease, or to death due to any cause. PFS will be censored at last adequate tumor assessment date showing non-PD or unconfirmed PD, or death happened from last adequate tumor assessment date showing non-PD, or if new anti-cancer treatment started. Patients who neither progressed or died, nor initiated any alternate anticancer therapy at time of data cutoff for study analysis or who are lost to follow-up, PFS will be censored at date of last documented response assessment.

Table 8.1: Censoring Scheme

Situation	Date of Progression	Outcome
No on study tumor assessments and no death/no new anti-cancer treatment within 12 weeks after first dose	Date of first dose (C1D1)	Censored
New anti-cancer treatment within 12 weeks after first dose without a prior reported progression or tumor assessment	Date of first dose (C1D1)	Censored
Death within 12 weeks after first dose or previous tumor assessment without progression and without subsequent anti-cancer therapy	Date of death	Death
PD/death or new anti-cancer treatment observed after 12 weeks from previous tumor assessment	Date of last tumor assessment performed before the PD/death or new anti-cancer treatment	Censored
Progression documented between scheduled visits within 12 weeks from previous tumor assessment.	Date of the first documented tumor progression	Progressed
New anticancer treatment started without a prior reported progression within 12 weeks from previous tumor assessment	Date of last tumor assessment performed before new anti-cancer treatment	Censored
On study tumor assessments but No progression, No death, No new anti-cancer treatment	Date of last adequate tumor assessment	Censored

PFS will be summarized using the Kaplan-Meier method for Arm 1 in a similar way as DoR defined in Section 8.2.1 along with progression free survival rates at different timepoints.

The same summary including Km plot for progression free survival will be repeated for subgroup HER2 status (HER2++ or HER2+++ vs HER2+), prior lines of treatment (≤2 vs ≥3) and prior use of enHERTU treatment (Yes vs No).

8.2.3. Overall Survival

Overall Survival (OS) will be calculated from the date of the first dose of study treatment to the date of death due to any cause. Patients who alive or lost to follow-up will be censored at the last documented date alive.

Overall survival will be summarized and presented using the Kaplan-Meier method in a similar way as DoR defined in Section 8.2.1 along with progression free survival rates at different timepoints but based on FAS.

The same summary including KM plot for progression free survival will be repeated for subgroup HER2 status HER2++ or HER2+++ vs HER2+), prior lines of treatment (≤2 vs ≥3) and prior use of enHERTU treatment (Yes vs No).

Responses and survival status will also be presented graphically with a Swimmer plot; each patient will be presented with one horizontal line, with the start and end of treatment, start and end of response, clinical progression and death marked where applicable.

9. Safety Analysis

All analyses of safety will be conducted using the safety analysis set, unless specified otherwise.

9.1. Adverse Events

An AE is defined as any untoward medical occurrence in a clinical study patient administered with a medicinal product and which does not necessarily have a causal relationship to study treatment.

A treatment-emergent AE (TEAE) is defined as an AE that meets any of the following conditions:

- begins on or after the first dose of study treatment.
- begins before the first dose of study treatment and worsens in severity on or after the first dose of study treatment.
- Lasts until 30 days after the last HER-Vaxx dose (for Arm2 also after last pembrolizumab dose)
- is completely missing a start date and stop date.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as explained in Section 4.0.

All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) according to MedDRA (Version 25.0).

An overview summary of AEs using number and percentage of patients and events for the following categories will be provided by treatment arms and overall. Percentages will be calculated using number of patients in the safety analysis set.

- Adverse Events (AEs)
- Treatment Emergent Adverse Events (TEAEs)
- Serious TEAEs
- Dose Limiting Toxicity (DLT)

- Grade 3 or higher TEAEs: will be showed by combining CTCAE grading and Intensity grading, where Intensity grading is for local injection site adverse events, while CTCAE grading is for other remaining adverse events
- Treatment-related TEAEs: will be showed separately for HER-Vaxx, Ramucirumab, Paclitaxel and Pembrolizumab
- Treatment-related serious TEAEs: will be showed separately for HER-Vaxx, Ramucirumab, Paclitaxel and Pembrolizumab
- TEAE leading to dose reduction or interruption: will be showed separately for HER-Vaxx, Ramucirumab, Paclitaxel and Pembrolizumab
- TEAE leading to treatment discontinuation: will be showed separately for HER-Vaxx, Ramucirumab, Paclitaxel and Pembrolizumab
- AE leading to death.
- Local Injection Reactions
- Immune Related Adverse Event (irAE)
- AE of Clinical Interest (AECI)

9.1.1. Incidence of Adverse Events

Summaries of the total number of TEAEs and the number and percentage of patients with at least one TEAE will be provided by treatment arms and overall. Treatment-emergent AEs will be presented by SOC and PT. Same tables will be repeated by PT (i.e., without SOC) separately. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated using number of patients in the safety analysis set.

TEAEs will be sorted in descending order of frequency of SOC based on the total of all treatment arms. Within each SOC, PTs will also be sorted in descending order of frequency of preferred terms. TEAEs will be sorted in descending order of frequency of PT based on the total of all treatment arms in the by PT (i.e., without SOC) table(s).

All AEs collected in the study will be presented in a listing including, but not limited to, verbatim term, preferred term, system organ class, NCI CTCAE/intensity grade and relationship to study treatment (HER-Vaxx, Ramucirumab, Paclitaxel and Pembrolizumab) using safety analysis set.

9.1.2. Relationship of Adverse Events to Study Treatment

A summary of related TEAEs to study treatment (HER-Vaxx only) will be presented in a table by incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study treatment. The possible relationships are ‘Definite’, ‘Probable’, ‘Possible’, ‘Unlikely’, ‘Not related’ and ‘Not applicable’. The ‘Related’ relation includes ‘Definite’, ‘Probable’, ‘Possible’. In the TEAE relationship table, if a patient reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented. Treatment emergent AEs that are missing a relationship or with a relationship other than listed will be presented in the summary table as “Related” but will be presented in the data listing with a missing relationship or the actual relationship respectively. Percentages will be calculated using number of patients in the safety analysis set.

A separate similar table will be created for related TEAEs associated with any treatment (HER-Vaxx, Ramucirumab, Paclitaxel and Pembrolizumab).

The related TEAE data will be categorized and presented by SOC, PT in a manner similar to that described in Section 9.1.1.

9.1.3. Severity of Adverse Event

A summary of TEAEs with Grade 3 or higher will be presented in a table. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible intensities for local injection site adverse events are "Absent (Grade 0)", "Mild (Grade 1)", "Moderate (Grade 2)", "Severe (Grade 3)" while possible gradings for other AEs are "Grade 1 (Mild)", "Grade 2 (Moderate)", "Grade 3 (Severe)", "Grade 4 (Life-threatening)" and "Grade 5 (Death)".

In the TEAE severity table, if a patient reported multiple occurrences of the same TEAE, only the most severe will be presented. Treatment-emergent AEs that are missing severity will be presented in tables as missing only. Percentages will be calculated using number of patients in the safety analysis set.

The TEAE with Grade 3 or higher data will be categorized and presented by SOC, PT in a manner similar to that described in Section 9.1.1. The same will be presented in another table for the TEAEs related to study treatment.

9.1.4. Serious Adverse Events

A serious AE (SAE) is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, is a congenital anomaly/birth defect, requires in-patient hospitalization or prolongation, or results in significant disability/incapacity.

A serious treatment-emergent AE (Serious TEAE) is defined as an SAE that meets any of the following conditions:

- begins on or after the first dose date of study treatment.
- begins before the first dose date of study treatment and worsens in severity on or after the first dose of study treatment.
- Lasts until 90 days after the last HER-Vaxx dose (for Arm2 also after last pembrolizumab dose)

Serious treatment-emergent adverse events (Serious TEAEs) will be presented in a table.

The treatment-emergent SAE data will be categorized and presented by SOC and PT in a manner similar to that described in Section 9.1.1.

A summary of treatment related serious TEAEs to study treatment (HER-Vaxx only) will also be presented in a table as mentioned in Section 9.1.2.

9.1.5. Adverse Events Leading to Treatment Discontinuation (HER-Vaxx only)

A summary of TEAEs where the answer to "Action Taken with HER-Vaxx" is "Permanently discontinued" will be presented in a table by SOC and PT in a manner similar to that described in Section 9.1.1. At each level of patient summarization, a patient is counted once if the patient

reported one or more events. Percentages will be calculated using number of patients in the safety analysis set.

9.1.6. Death

A summary of AEs where the answer to "Outcome" is "Death" will be presented in a table by SOC and PT in a manner similar to that described in Section 9.1.1. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated using number of patients in the safety analysis set.

9.1.7. DLT

A listing of DLTs will also be reported for the safety run-in phase of Arm 1 and 2.

9.2. Clinical Laboratory Evaluations

Laboratory assessments will be performed by a local laboratory. All summaries and listings will be presented in SI units.

All clinical laboratory test results will be summarized using descriptive statistics or frequency table and also presented in listings by treatment arm, patient and visit using safety analysis set. The numeric results will be presented for observed and change from baseline values.

All relevant clinical laboratory tests results will be classified as Low, Normal, and High, or Normal/Abnormal according to the normal ranges, and will be presented in listings.

The numeric parameters will be graded using CTCAE v5.0, for applicable tests. Shift in toxicity grades from baseline to worst post-baseline will be presented in a table.

If any laboratory value falls above or below the upper or lower level of quantification, the value of the upper or lower level of quantification will be taken (e.g., <0.2 will become 0.2) for summaries but left as recorded in the listing. If multiple results fall on the same visit, these will be handled as per the rules mentioned in Section 4.

9.2.1. Hematology

Hematology includes complete blood count (CBC), including red blood cell (RBC) count, hemoglobin, hematocrit, reticulocyte count, white blood cell (WBC) count with differential (neutrophils, bands, eosinophils, basophils, lymphocytes, monocytes, and other cells), platelet count, and C-reactive protein (CRP). Descriptive statistics, CTCAE shift tables and listing will be presented as described in Section 9.2.

9.2.2. Serum Chemistry

Serum chemistry includes Blood urea nitrogen (BUN) or urea, creatinine, sodium, chloride, potassium, magnesium, bicarbonate, calcium, phosphorus, total protein, albumin, alkaline phosphatase, glucose, total bilirubin, direct and indirect bilirubin, lactate dehydrogenase (LDH), cholesterol, uric acid, triglyceride levels, gamma glutamyl transpeptidase (GGT), AST, and ALT. Descriptive statistics, CTCAE shift tables and listing will be presented as described in Section 9.2.

9.2.3. Thyroid Function Test

Thyroid Function test includes thyroid stimulating hormone (TSH) and free thyroxine (free T4). Additional tests may be requested by the investigator in case of abnormal TSH and/or free T4. Descriptive statistics, CTCAE shift tables and listing will be presented as described in Section 9.2.

9.2.4. Serology

Serology includes HBsAg reactive, Hepatitis C virus antibody and HIV 1/2 antibodies. A summary table and listing will be presented as described in Section 9.2.

9.2.5. Pregnancy

A listing will be provided for Pregnancy test based on safety analysis set.

9.3. Vital Sign Measurements

Summary tables presenting observed values and changes from pre-dose to post-dose will be presented for vital sign data, including height (cm), weight (kg), BSA (m^2), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), heart rate (beats/min), respiratory rate (breaths/minute) and temperature (°C) by treatment arms and visit for the patients in the safety analysis set. All vital sign result will be presented in a listing by treatment arms, patient and visit using safety analysis set.

9.4. Physical Examination

The status of a body system and any finding associated with the body system as normal, abnormal (clinically significant), abnormal (not clinically significant), not done or not applicable will be captured as per schedule of events (Appendix 13.2). Physical examination results will be presented in a listing by treatment arms, patient and visit using safety analysis set.

9.5. ECOG

Number and percentage of ECOG (Eastern Cooperative Oncology Group) performance status will be summarized by treatment arms and visit using safety analysis set. Shifts from baseline to the EOT visit in ECOG performance status also will be summarized. A listing of ECOG performance grade will be provided by treatment arms, patient and visit using safety analysis set.

9.6. LVEF

Actual value and change from baseline in LVEF (%) will be summarized descriptively by treatment arms and scheduled visit using safety analysis set. A listing of LVEF data will also be provided by treatment arms, patient and visit using safety analysis set.

9.7. Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed at the time points as scheduled (Appendix 13.2).

ECG result values and changes from baseline will be summarized descriptively for all ECG parameters including heart rate (beats/minute), PR Interval (msec), QRS Duration (msec), QT Interval (msec) by treatment arms for patients in the safety analysis set. Interpretation will be

presented with number and percentage of patients by treatment arms and overall and visit using safety analysis set.

All ECG results and interpretation will be presented in a listing by treatment arms, patient and visit using safety analysis set.

9.8. Immunogenicity

This analysis will be performed using FAS. The level of HER2-specific antibodies and immune phenotyping will be assessed in peripheral blood at baseline and at the timepoints as per Appendix 13.2 while on treatment.

Values and changes from baseline in immunological data will be summarized by treatment arm and visit. Descriptive statistics (minimum, maximum, median, geometric mean, geometric mean 95% CI, arithmetic mean, standard deviation and Q1, Q3) for actual value and fold rise over baseline in HER2-specific antibodies (includes Analysis of HER2/neu expression, PD-L1 expression and TMB in pre- and post-treatment tumor biopsies / liquid biopsies (circulating tumor DNA [ctDNA]/next generation sequencing [NGS])) and immune phenotyping will be tabulated by scheduled visit and treatment arms. If results are reported as lower than the minimal limit of assay detection, a value equal to half of the minimal limit of assay detection will be imputed in the calculation.

Geometric mean titer (GMT) will be calculated as anti-logarithm of $\sum$ (log-transformed titer/number of patients with titer information). The 95% CI for GMT will be calculated as the anti-log transformation of upper and lower limits for a 2-sided CI of the mean of the log-transformed titers.

Geometric mean fold rises (GMFR) will be calculated as anti-logarithm of $\sum$ [log-transformed titer ratio of Yi/Bi)/number of patients with titer information], where Yi is the post-dose titer and Bi is the baseline titer for patient i. The same data summaries will be provided as GMT.

Listings of HER2-specific antibodies and immune phenotyping data will be provided using full analysis set.

Associations between immunologic endpoints with clinical outcomes (ORR, OS, PFS and DoR) will be assessed by graphical techniques using box plot and scatter plot.

Analyses of cellular immunogenicity data are conducted by Imugene and is documented separately.

10. Interim Analysis

This study is designed as a 2- Stage study. Each Arm will be evaluated independently.

For each Arm, after 8 evaluable patients are enrolled (Stage 1) an additional 7 evaluable patients will be enrolled in that Arm (Stage 2) if 1 or more patients respond (i.e., experience CR or PR). If there are no responses in Stage 1, then preliminary anti-tumor activity in the group will not have been identified and no further patients will be enrolled in that Arm. If the Arm continues to Stage 2, a total of 15 evaluable patients will be studied for that Arm. The Arm will be considered successful if ≥ 4 treated patients respond, and the Arm may be expanded to enroll 25 patients. This design is applied to both arms and is based on a 2-Stage Simon Minimax design for a total of 15

evaluable patients (null hypothesis that ORR ≤ 11% versus the alternative hypothesis that ORR ≥ 40% with alpha=0.07268 and power=90.463%).

The list of Tables, Listings and Figures for Interim analysis are available in Appendix 13.3.

11. Changes in the Planned Analysis

The following are the change in the planned analysis.

- Duration of response is defined as the time from the first observation of CR or PR to first documented progressive disease (PD) (confirmed after follow-up scan), or death due to any cause in protocol, but SAP consider it as the time from the first observation of CR or PR to first documented progressive disease (PD) or death due to any cause.
- Progression Free Survival (PFS) is defined as the time from the first dose date of study treatment to first observation of documented progressive disease (PD; that is confirmed by a follow up scan), or to death due to any cause in protocol, but SAP consider it as the time from the first dose date of study treatment to first observation of documented progressive disease, or to death due to any cause.

12. References

- Brookmeyer, R. and Crowley, J. (1982) A confidence interval for the median survival time. Biometrics, 38, 29-41. doi:10.2307/2530286.
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- Shiroiwa T, Fukuda T, Shimozuma K. Cost-effectiveness analysis of trastuzumab to treat HER2-positive advanced gastric cancer based on the randomised ToGA trial. Br J Cancer, 2011;105(9):1273-8.
- Wilson, E. B. (1927), “Probable Inference, the Law of Succession, and Statistical Inference,” Journal of the American Statistical Association, 22, 209–212.

13. Appendices

13.1. Algorithm for Confirmed Best Overall Response (CBOR) according to RECIST v1.1

1. The best overall response is determined once all the data for the patient is known and is defined as the best confirmed response, recorded between the date of first dose and the date of the initial objectively documented Tumor progression by the investigator or the date of subsequent therapy, whichever occurs first. For patients without documented progression or subsequent therapy, all available response will contribute to the CBOR determination. The Tumor responses up to progressive disease (PD) will only be considered for CBOR. The evaluations after PD will not be considered.
2. Subsequent assessments for BOR confirmation should be performed no less than 4 weeks in between (the sufficient time period is defined on the strength of the schedule of Tumor assessments). Patients need to have two consecutive assessments of PR or CR to be a responder. As per the study requirement and Schedule of Events defined in Appendix 13.2, Tumor imaging assessment is planned at every 8 weeks ± 7 days.
3. In the case of a stable disease, the follow-up measurements must meet the stable disease criteria at least once after the study entry at a minimum interval (usually 6 – 8 weeks) similar to the unconfirmed BOR case.
4. Determine the first time point response as the first assessment of the non-confirmed best response (CR > PR > SD > PD) for a patient, then take the first occurrence of the non-confirmed best response and look at the subsequent assessments within the considered period using the following rules given in Table 13-1.
5. A special case takes place when NE time point assessments occurred. For example, it makes sense to consider the following chain of responses PR – NE – PR as a confirmed Partial Response.
6. The following table, based on Appendix from the RECIST v1.1 guidelines, summarizes the algorithm describing how Confirmed Response is determined from the overall Tumor assessments as assessed by the local Investigator's review.

Table 13-1: Confirmed Best Overall Response Algorithm (RECIST v1.1)

Overall Response first time point	Overall response at subsequent time point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response 'SD' would depend on whether minimum duration for SD was met, otherwise PD.

		However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR
CR	SD	SD or PD SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD or PD SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD or NE SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD or PD SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD or NE SD provided minimum criteria for SD duration met, otherwise, NE
SD	SD	SD
SD	PD	SD or PD SD provided minimum criteria for SD duration met, otherwise, PD
SD	NE	SD or NE SD provided minimum criteria for SD duration met, otherwise, NE
CR, PR, SD	Missing or No further assessment	SD or NE SD provided minimum criteria for SD duration met, otherwise, NE
PD	Missing or No further assessment	PD. Ignore all assessments after initial overall response of PD.
NE	NE	NE
NE	Missing or No further assessment	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

13.2. Schedule of Study Procedures

13.2.1. Table 1: Schedule of Activities Arm 1 (HER-Vaxx + Chemotherapy)

Cycle	Screening (S)	Cycle 1 (T)				Cycle 2 (T)				Cycle 3 Onwards (T)				End of Treatment (E)	Survival Follow Up (U)
Day	D-21 to D-1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22		
Cumulative Day	D-21 to D-1	1	8	15	22	29	36	43	50	57	64	71	78		
Visit window	-	-	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 7d)	(+/- 7d)
Informed Consent	X														
Eligibility	X	X(A)													
Tumor biopsy (B)	X					X								X	
Demographics	X														
Medical History	X														
Physical Exam (C)	X	X	X	X	X	X	X	X	X	X(C)	X	X	X	X	
Weight & Vital Signs(D)	X	X	X	X	X	X	X	X	X	X(D)	X	X	X	X	
Height	X									-					
ECOG	X	X								-				X	
Radiographic Assessment(F)		X	X(F)												
Cardiac Assessment(G)	X									C4D1(G)				X	
Pregnancy Test (H)	X	X				X				X(H)				X	
HIV, Hepatitis B/C (I)	X									-					
Hematology, Chemistry(J)	X	X	X	X	X	X	X	X	X	X(J)	X	X	X	X	
Thyroid Function Tests(K)	X	X								X(K)				X	

Cycle	Screening (S)	Cycle 1 (T)				Cycle 2 (T)				Cycle 3 Onwards (T)				End of Treatment (E)	Survival Follow Up (U)
Day	**D-21 to D-1**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**		
Cumulative Day	**D-21 to D-1**	**1**	**8**	**15**	**22**	**29**	**36**	**43**	**50**	**57**	**64**	**71**	**78**		
Visit window	**-**	**-**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 3d)**	**(+/- 7d)**	**(+/- 7d)**
Exploratory Biomarker (L)		X	X		X			X		X(L)				X	
Immunology – humoral (M)		X	X		X			X		X				X	X
Immunology – cellular (N)	X	X	X		X			X		X(N)				X	
ctDNA (O)		X				X				X				X	
HER-Vaxx (P)		X		X		X				X(P)					
Ramucirumab(Q)			X		X		X		X		X		X		
Paclitaxel(Q)			X	X	X		X	X	X		X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events(R)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X(R)
Survival/ anti-cancer treatment															X

Table 1 Footnotes

A. If screening assessments (Hematology, Blood Chemistry, Thyroid Function Test, Eastern Cooperative Oncology Group [ECOG], Cellular Immunology & Pregnancy Test) are performed within 72 hours of the first study treatment administration, the assessments do not have to be repeated on Cycle 1, Day 1.
B. Documentation of HER-2 positivity at diagnosis is required. A screening visit or archival tumor biopsy (either fresh or archival tissue) or post-progression pathology report should be provided. Cycle 2 and End of Treatment tumor biopsies are optional. The Cycle 2 optional tumor biopsy can be taken on any day during Cycle 2.
C. A limited, symptom-directed physical examination may be performed post Cycle 1, Day 1. Physical exam to be performed at each HER-Vaxx and chemotherapy treatment visit. In HER-Vaxx treatment cycles (C3 C5, C7..), physical exam to be performed at each visit in the cycle (while chemotherapy continues). In non-HER-Vaxx treatment cycles (C4, C6 C8 ..), physical exam not required at D1, but required at D8, D15, D22 (while chemotherapy continues).

D. Weight and Vital Signs (blood pressure, respiratory rate, heart rate and temperature) to be recorded prior to receiving study treatment. In addition, record temperature 30 min (±10 mins) after each HER-Vaxx vaccination. For Arm 1, weight to be used for body surface area (BSA) calculation as per institutional practice. Weight & vital signs must be performed at each HER-Vaxx and chemotherapy treatment visit. In HER-Vaxx treatment cycles (C3 C5, C7..), weight & vital signs to be performed at each visit in the cycle (while chemotherapy continues). In non-HER-Vaxx treatment cycles (C4, C6 C8 ..), weight & vital signs not required at D1, but required at D8, D15, D22 (while chemotherapy continues).
E. The end of treatment (EoT) visit will be completed at least 30 days after last study treatment.
F. Radiographic assessments: Cycle 1 assessment can be performed up to 14 days prior to Cycle 1 Day 1 and then every 6 weeks from Cycle 1, Day 1 within a +/- 3 day window until disease progression, or withdrawal for any other reason. Radiographic assessment is according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 response criteria. Upon PD, a scan will be scheduled 4 to 6 weeks after initial PD scan to confirm progression. After discontinuation from the study for any reason other than disease progression, radiographic change will be collected every 12 weeks until determination of progressive disease.
G. Cardiac assessment includes 12-lead ECG and echocardiography or multiple gated acquisition (MUGA) scan. Assessment to be performed at Screening, Cycle 4, Day 1 and then Day 1 every 3 cycles and EoT. Significant abnormal cardiac assessments should be evaluated by a cardiologist.
H. Highly sensitive urine pregnancy test (sensitivity of at least 25 mIU/mL) for all female patients of childbearing potential will be collected once each cycle prior to study treatment and/or chemotherapy:
    - on Day 1 of each odd-numbered cycle, starting Cycle 3.
    - on Day 8 of each even-numbered cycle, starting Cycle 4.

   If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Treatment may be delayed until negative beta-human chorionic gonadotrophin (BHCG) blood test is received.
I. Testing for human immunodeficiency virus (HIV), Hepatitis B and Hepatitis C is not required unless mandated by a local health authority.
J. Local hematology and chemistry laboratory testing to be collected prior to receiving any study treatment. Local labs can be drawn up to 72 hours before any on-study clinic visit. Local labs to be taken at each HER-Vaxx and chemotherapy treatment visit. In HER-Vaxx treatment cycles (C3, C5, C7, etc.), safety labs are to be taken at each visit in the cycle (while chemotherapy continues). In non-HER-Vaxx treatment cycles (C4, C6, C8, etc.), safety labs are not required at D1, but are required at D8, D15, D22 (while chemotherapy continues).
K. Thyroid function test to be performed prior to receiving study treatment. Thyroid function test is performed on Day 1 every 2nd cycle from Cycle 3 onward.
L. Whole blood for exploratory biomarkers (all exploratory biomarkers except ctDNA which is captured separately per footnote O) to be collected prior to administration of study treatment. Exploratory biomarkers to be collected on Day 1 every 2nd cycle from Cycle 3 onward.
M. Whole blood for humoral immunity samples to be collected prior to administration of study treatment. Blood samples for humoral immunity to be collected on Day 1 of every cycle from Cycle 3 onward and every 12 weeks for up to 1 year during Survival Follow Up.
N. Whole blood for cellular immunity peripheral blood mononuclear cell (PBMC) samples to be collected prior to administration of study treatment. Cellular immunity samples to be collected on day 1 of every 2nd cycle from Cycle 3 onward.
O. Whole blood for ctDNA HER-2 genotyping will be collected prior to administration of study treatment on Day 1 of every cycle.
P. HER-Vaxx to be administered as indicated for Cycles 1 through 3 and on Day 1 of every 2nd cycle from Cycle 3 (i.e. Cycles 3, 5, 7, …) onward until treatment discontinuation criterion is met. Patients to be observed for 30 minutes post HER-Vaxx administration. Note: Please ensure that HER-Vaxx is administered at least 48 hours before starting paclitaxel (when scheduled on the same day).

Q. Ramucirumab 8 mg/kg IV on Days 8 and 22 of a 28-day cycle + paclitaxel 80 mg/m^2 on Days 8, 15, and 22 of a 28-day cycle, for as long as clinically indicated. Paclitaxel to be administered at least 48 hours after administration of HER-Vaxx (when scheduled on the same day).
R. During Survival Follow-Up serious adverse events (SAEs) considered related to study treatment are to be reported 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.
S. Screening can occur across multiple clinic visits within the 21-day screening period.
T. Each cycle is 28 days.
U. After study discontinuation and completion of the End of Treatment visit, patients will be followed for survival every 12 weeks (± 7 days) for up to 3 years.

13.2.2. Table 2: Schedule of Activities Arm 2 (HER-Vaxx + Pembrolizumab)

Cycle	Screening (T)	Cycle 1 (U)				Cycle 2 (U)		Cycle 3 (U)	Cycle 4 Onwards (U)	End of Treatment (F)	Survival Follow Up (V)
Day	D -21 to D -1	Day 1	Day 8	Day 15	Day 22	Day 1	Day 15	Day 1	Day 1		
Cumulative Day	D-21 to D-1	1	8	15	22	29	43	50	71		
Visit window	-	-	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 3d)	(+/- 7d)	(+/- 7d)
Informed Consent	X										
Eligibility	X	X(A)									
HER2+ Assessment(B)	X										
Tumor biopsy (C)	X					X				X	
Demographics	X										
Medical History	X										
Physical Exam (D)	X	X	X	X		X		X	X	X	
Weight and vital signs (E)	X	X	X	X		X		X	X	X	
Height	X										
ECOG	X	X								X	
Radiographic Assessment(G)		X	X(G)								
Cardiac Assessment(H)	X								X(H)	X	
Pregnancy Test (I)	X	X				X		X	X	X	
HIV, Hepatitis B/C (J)	X										
Hematology, Chemistry(K)	X	X	X	X		X		X	X	X	
Thyroid Function Tests(L)	X	X					X		X(L)	X	
Exploratory Biomarker (M)		X	X		X		X		X(M)	X	
Immunology – humoral (N)		X	X		X		X		X	X	X
Immunology – cellular (O)	X	X	X		X		X		X(O)	X	
ctDNA (P)		X				X		X	X		
HER-Vaxx (Q)		X		X		X		X(Q)			
Pembrolizumab(R)			X			X		X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	
Adverse Events(S)	X	X	X	X	X	X	X	X	X	X	X(S)
Survival/anti-cancer treatment											X

Table 2 Footnotes

A. If screening assessments (Hematology, Blood Chemistry, Thyroid Function Test, Eastern Cooperative Oncology Group [ECOG], Cellular Immunology, & Pregnancy Test) are performed within 72 hours of the first study treatment administration, the assessments do not have to be repeated on Cycle 1, Day 1.
B. Human epidermal growth factor receptor 2 (HER2/neu+) assessment prior to enrollment. Confirmed HER2/neu overexpression (3+ by immunohistochemistry (IHC) or if IHC 2+ confirmed by fluorescent in situ hybridization [FISH], brightfield double in situ hybridization [BDISH] or chromogenic *in situ* hybridization [CISH]) using post-progression fresh or archival tissue, or post-progression pathology report. Sponsor may approve inclusion based on liquid (blood based) biopsy to assess patients' HER2/neu positivity where tumor biopsy is not clinically indicated.
C. A post-progression fresh or archival tumor biopsy sample or post-progression pathology report will be obtained for all patients to confirm eligibility. Cycle 2 and End of Treatment tumor biopsies are optional. The optional tumor biopsy can be taken on any day during Cycle 2.
D. A limited, symptom-directed physical examination may be performed post Cycle 1, Day 1. The physical exam must be performed prior to receiving any study treatment.
E. Weight and Vital Signs (blood pressure, respiratory rate, heart rate and temperature) to be recorded prior to receiving study treatment. In addition, record temperature 30 min (±10 mins) after each HER-Vaxx vaccination.
F. The end of treatment (EoT) visit will be completed at least 30 days after last study treatment.
G. Radiographic assessments: Cycle 1 assessment can be performed up to 14 days prior to Cycle 1, Day 1 within a +/- 3 day window and then every 6 weeks from Cycle 1, Day 1 until disease progression, or withdrawal for any other reason. Radiographic assessment is according to response evaluation criteria in solid tumors (RECIST) version 1.1 response criteria. Upon PD, a scan will be scheduled 4 to 6 weeks after initial PD scan to confirm progression. After discontinuation from the study for any reason other than disease progression, radiographic change will be collected every 12 weeks until determination of progressive disease.
H. Cardiac assessment includes 12-lead ECG and echocardiography or multiple gated acquisition (MUGA) scan. Assessments to be performed at Screening, Cycle 4 Day 1, then every 4 cycles and at EoT. Significant abnormal cardiac assessments should be evaluated by a cardiologist.
I. Highly sensitive urine pregnancy test (sensitivity of at least 25 mIU/mL) for all female patients of childbearing potential will be collected once each cycle prior to study drug treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Treatment may be delayed until negative beta-human chorionic gonadotrophin (BHCG) blood test is received.
J. Testing for Human Immunodeficiency Virus (HIV), Hepatitis B and Hepatitis C is not required unless mandated by a local health authority.
K. Local hematology and chemistry laboratory testing to be collected at each study treatment visit prior to receiving any study treatment. Local labs can be drawn up to 72 hours before any on-study clinic visit.
L. Thyroid function test to be performed prior to receiving study treatment. Thyroid function test to be performed on day 1 every 2nd cycle from Cycle 4 onward (i.e., cycles 4, 6, 8, 10…).
M. Whole blood for exploratory biomarkers (all exploratory biomarkers except ctDNA which is captured separately per footnote O) to be collected prior to receiving study treatment. Exploratory biomarker samples to be collected every 3rd cycle from Cycle 4 onward (i.e., cycles 4, 7, 10…).
N. Humoral samples to be collected prior to receiving study treatment. Blood samples for humoral immunity to be collected on Day 1 of every cycle from Cycle 4 onward and every 12 weeks for up to 1 year during Survival Follow Up.
O. Cellular immunity peripheral blood mononuclear cell (PBMC) to be collected prior to receiving study treatment. Cellular immunity samples to be collected every 3rd cycle from Cycle 4 onwards.

P. Whole blood for ctDNA HER-2 genotyping will be collected prior to administration of study treatment on Day 1 of every cycle.
Q. HER-Vaxx to be administered as indicated for Cycles 1 through 3 and on day 1 of every 3rd cycle from Cycle 3 onward (i.e., cycles 3 6, 9, 12…) until treatment discontinuation criterion is met. Patients to be observed for 30 minutes post HER-Vaxx administration. Note: Please ensure that HER-Vaxx is administered at least 30-60 minutes before starting pembrolizumab (when scheduled on the same day).
R. Pembrolizumab 200 mg administered until treatment discontinuation criterion met for a maximum of 35 cycles. Pembrolizumab to be administered at least 30-60 minutes following administration of HER-Vaxx (when scheduled on the same day).
S. During Survival Follow-Up Serious adverse events (SAEs) considered related to study treatment are to be reported 90 days after the final dose of study treatment or until initiation of new systemic anti-cancer therapy, whichever occurs first.
T. Screening can occur across multiple clinic visits within the 21-day screening period.
U. Cycle 1 is 28 days. Cycles from Cycle 2 onwards are 21 days.
V. After study discontinuation and completion of the End of Treatment visit, patients will be followed every 12 weeks (± 7 days) for up to 3 years.

13.3. Table of Contents for Table, Listing and Figure

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3	Table	Table 14.1.1.3 Significant Protocol Deviations	Safety Analysis Set	
4	Table	Table 14.1.2.1 Demographics and Baseline Characteristics	Safety Analysis Set	Y
5	Table	Table 14.1.3.1 Medical History	Safety Analysis Set	
6	Table	Table 14.1.3.2 Oncology and Surgical History	Safety Analysis Set	Y
7	Table	Table 14.1.4.1 Prior Medication	Safety Analysis Set	Y
8	Table	Table 14.1.4.2 Concomitant Medications	Safety Analysis Set	Y
9	Table	Table 14.1.4.3 Prior Drug Therapies and Medications	Safety Analysis Set	
10	Table	Table 14.1.4.4 Concomitant Drug Therapies and Medications	Safety Analysis Set	
11	Table	Table 14.1.4.5 Prior and Concomitant Radiotherapies	Safety Analysis Set	
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15	Table	Table 14.2.1.2 Summary of Duration of Confirmed Response using KM Method – RECIST v1.1	Evaluable Analysis Set	Y
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19	Table	Table 14.2.1.3 Summary of Progression Free Survival using KM method – RECIST v1.1	Evaluable Analysis Set	Y
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